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| 09/935,916 | 08/23/2001 | Constantine Stratakis | NIH-05098 | 1614 |

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/935,916

Applicant(s)

STRATAKIS ET AL.

Examiner

Jeffrey Fredman

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 1, 2 and 4-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status

Claims 1-38 are pending.

Claim 3 is rejected.

Claims 1, 2, 4-38 are withdrawn from consideration.

Sequences other than SEQ ID NO: 41 are withdrawn from consideration.

Election/Restrictions

1. Applicant's election with traverse of Group I and of SEQ ID NO: 41 in the paper filed March 12, 2003, is acknowledged. The traversal is on the ground(s) that there is overlap between the subject matter of the groups. This is not found persuasive because the issue is not "overlap" but distinctness. As the restriction explicitly made clear, the inventions are distinct. Further, with regard to search, there is no overlap since the separate classification is prima facie evidence of burden which has not been rebutted. Further, the search for each group would be different and would identify and rely upon different prior art.

With regard to the argument that there is no burden of search relative to the different DNA sequences because a single search would identify all of the relevant art, this statement is not correct. Each sequence is drawn to a different polymorphism which will require specific search and examination relating to that polymorphism. The analysis and search will be different for each polymorphism and different art will necessarily need to be reviewed. The specification at page 5 expressly notes that these polymorphisms may be associated not only with Carney complex but also with

endocrine tumors, pigmentation defects and other types of cancers. Since each polymorphism may be responsible for a different, or no, syndrome, a separate search and examination is required for each sequence. Applicant will be required to cancel the non-elected sequences prior to allowance.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed July 23, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112 – Indefiniteness

3. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

SEQ ID NO: 41 of claim 3 is indefinite when read in light of the specification. The specification discussed SEQ ID NO: 41 as having a two nucleotide deletion. However, SEQ ID NO: 41 has only a one nucleotide deletion. Therefore, it is indefinite if SEQ ID NO: 41 is simply wrong in both the specification and sequence listing, or if it is intended to reflect some alternate mutation. Therefore, two different rejections are made depending upon whether SEQ ID NO: 41 is incorrect and is intended to be 578delTG or if SEQ ID NO: 41 is correct and is intended to reflect a new mutation. The art rejection

assumes that the claim is intended to address 578delTG and SEQ ID NO: 41 is incorrect. The enablement rejection addresses the possibility that SEQ ID NO: 41 is correct and is a new mutation different than 578delTG.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claim is drawn to a nucleotide sequence comprising SEQ ID NO: 41. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claim is relatively narrow and, as elected, is drawn only to mutant nucleic acids comprising SEQ ID NO: 41.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is a significant discrepancy between the sequence claimed and the sequence indicated by the prior art as being associated with Carney complex. In particular, Kirschner et al (*Human Mol. Genetics* (2000) 9(20):3037-3046) shows the sequence of a 578delTG mutation in figure 4. This sequence differs from SEQ ID NO: 41 in that SEQ ID NO: 41 has a deletion of only the G. SEQ ID NO: 41 is NOT at TG deletion but rather only a G deletion. Consequently, it would require a significant amount of experimentation to determine the effect of the single nucleotide deletion relative to the two nucleotide deletion which is the focus of the prior art and of the specification.

The unpredictability of the art and the state of the prior art

The art teaches that there is a two base pair mutation, either at 578delTG (see Kirschner et al (*Human Mol. Genetics* (2000) 9(20):3037-3046)) or deletion of a TG at positions 576-577 (see page R34, column 2 of Casey et al (*J. Clin. Invest.* (August 5,

2000) 106:R31-38)). The presence and effect of nucleotide polymorphisms is extremely unpredictable. This is shown by the unpredictable linkage analysis in Kirschner, where the Carney gene was first linked to 2p16 before the correct association with 17q22-24 and the PRKAR1A gene was identified. In this case, where SEQ ID NO: 41 has only a single nucleotide deletion, instead of the two nucleotide deletion discussed in the specification and shown in the prior art, it is entirely unpredictable what effect this single nucleotide deletion would have. This single nucleotide deletion is NOT associated with Carney complex and has no other particular use. (Though for utility purposes under 35 U.S.C. 101, it is noted that the sequence could be used to detect the PRKAR1A gene). Therefore, in light of the conflicting teachings in the specification and prior art which require two nucleotide deletions relative to the single nucleotide deletion found in SEQ ID NO: 41, the use of this sequence would be extremely unpredictable.

Working Examples

The specification has a working example with the two nucleotide deletion but has no working examples where a patient is shown to have the single nucleotide deletion of SEQ ID NO: 41.

Guidance in the Specification.

The specification is contradictory, since it teaches SEQ ID NO: 41, but seems to indicate that this is also 578delTG. Therefore, the specification fails to clearly guide the practitioner in how to use the mutation of SEQ ID NO: 41 since the specification does not clearly delineate what is the mutation being claimed.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching of the specification and art conflict on what is the 578delTG mutation relative to SEQ ID NO: 41. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the internally conflict in the specification relative to a claim in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the what the mutation is and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to use the sequence in the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claim 3 is rejected under 35 U.S.C. 102(a) as being anticipated by Casey et al (J. Clin. Invest. (August 5, 2000) 106:R31-R38).

Casey teaches a nucleotide sequence of a mutant protein kinase regulatory subunit 1A, wherein said mutation is 578delTG (See page R34 at column 2, last sentence to column 3). Further, Casey teaches that the sequence was amplified (see page R32, column 2) and the amplified sequence from the patients with the disease would inherently comprise SEQ ID NO: 41.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman
Primary Examiner
Art Unit 1634

May 28, 2003